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THE RELATIONSHIP OF THE PNEUMOCOCCUS TO ACUTE INFECTIONS OF THE UPPER RESPIRATORY TRACT IN MAN*

INFLUENZA STUDIES VI

J. E. GORDON

From the Department of Hygiene and Bacteriology, University of Chicago

In the present study, two general groups of acute respiratory infection have been investigated. The first group included a number of simple acute respiratory infections of varied clinical type, occurring in an urban population, and broadly classified as "common colds." The second was a recurrent epidemic of influenza occurring in the early winter months of 1920 and characterized by the same general clinical picture which was manifested in the great wave of influenza pandemic in 1918. The purpose of the work was to determine, first, the frequency with which the pneumococcus could be demonstrated in cases of influenza and in waves of common colds, and then to compare the extent of its incidence in these conditions with its occurrence in the upper respiratory tract of normal persons.

In the event that the pneumococcus was present to a greater extent in the pathologic respiratory tract than in the normal, it was essential to determine whether those pneumococci represented a single like strain in a given group of cases, or whether they were heterologous in nature and representative of unrelated varieties of that organism. Likewise, the pneumococcus isolated from the site of the primary lesion in common colds and influenza possesses a number of possibilities in its relationship to the infection. It may be present there normally as a part of the normal bacterial flora of that region and be involved in no way with the infection. It may, although normally present, be playing an accessory rôle in the inflammation. Again, it may be present as a secondary invader to the bacterium or virus causing the original infection. Lastly, it may be the true etiologic agent involved in the inflammation.

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With these various possibilities in mind, it was hoped by the general procedure outlined to acquire a certain amount of information bearing on the rôle of the pneumococcus in the etiology of "common colds" and influenza.

BIOLOGIC DIFFERENCES AMONG PNEUMOCOCCI

The study of the pneumococci isolated from patients with common colds and influenza and from normal persons, and the search for a particular organism which might be habitually concerned in the etiology of a given infection, has been largely facilitated by the advance, within the last few years, of our knowledge of the biology of the pneumococcus. It has been demonstrated that there exists within the species, certain well differentiated groups or types distinct one from the other.

Eyre and Washbourn,[1] in testing a serum made by Pane,[2] an Italian worker, for antibodies which would protect white mice against lethal doses of certain stock strains of pneumococci, found that in only 2 of 5 cases would this serum protect against his strains of cocci. Protection was not afforded against the other 3 in any appreciable dilution. This was the first indication of a biologic difference in strains of pneumococci.

Some years later Park and Williams[3] showed that the organism described originally by Schottmüller[4] as Streptococcus mucosus was really a pneumococcus, judged by its biologic properties, and should be classified as such, although differing morphologically from other varieties of pneumococci. Added evidence tending to include these organisms among the pneumococci was furnished by Collins[5] through specific agglutination and agglutinin absorption tests. She furthermore contributed data tending to show that pneumococci in general could be separated into various groups by means of their agglutinative properties. Added observations by Hanes[6] show decisively that these organisms are pneumococci, and that there is distinct cross agglutination among various members of the group. Neufeld and Händel[7] demonstrated that there were well established varieties of pneumococci which, though resembling each other morphologically, nevertheless showed distinct immunologic differences. The work of Neufeld and Händel was followed by a more detailed study by Cole[8] and by Dochez and Gillespie,[9] the latter workers dividing pneumococci into 4 types or groups. These groups they designated as types 1, 2, 3 and 4. Types 1 and 2 differed from each other only slightly in morphology, but immunologically they were entirely distinct. These immunologic differences they demonstrated by animal protection and by agglutination tests. Group 3 included those organisms designated as Pneumococcus mucosus and were distinct from other pneumococci morphologically and serologically, although agreeing among themselves as a group. Group 4 was a heterologous division and included all cultures which did not fall into one of the other 3 groups. They resemble the organisms of types 1 and 2 morphologically, but do not possess common agglutinative properties either with the other groups or among themselves. This classification has been substantiated by subsequent investigations, those of Lister,[10] Mathers,[11] Clough,[12] Hartman and Lacy,[13] Richardson,[14] and Armstrong [15] among others.

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[1] Brit. Med. Jour., 1899, 2, p. 1247.

[2] Centralbl. f. Bakteriol., 1897, 21, p. 664.

[3] Jour. Exper. Med., 1905, 7, p. 403.

[4] München. med. Wchnschr., 1903, 50, p. 849.

[5] Jour. Exper. Med., 1905, 7, p. 420.

[6] Ibid., 1914, 19, p. 38.

[7] Arb. a.d.k. Gesndhtsamte, 1910, 34, p. 293.

[8] Arch. Int. Med., 1914, 14, p. 56.

[9] Jour. Am. Med. Assn., 1913, 61, 727.

Later work by Avery [16] on the classification of the group, showed that there were certain strains of pneumococci which reacted atypically when agglutinated with type 2 serum in that there occurred a partial or delayed reaction. Closer study led to a separation of these atypical type 2 strains into 2 well-defined serologic subgroups, type 2 a and 2 b with a heterologous subgroup type 2 x. Avery's experiments were extended by Stillman,[17] and study of a larger number of such strains proved that atypical type 2 organisms could be subdivided into at least 12 different subgroups. In fact, it would seem that there is really evidenced within this group a repetition of what has occurred in the whole series. Type 2 has a tendency to variation inherited from the original coccus, with one of the subgroups type 2 m still showing tendencies to subdivide.

Attempts to show some agreement among the heterologous type 4 strains failed to demonstrate distinct division into subgroups. Fourteen strains studied by Dochez and Gillespie,[9] seem generally to represent distinct varieties (Cole [8]). Olmstead,[18] however, reports, from a study of 213 group 4 strains, that they can be divided into about 12 subgroups by cross agglutination experiments.

METHODS OF STUDY

The method of collecting material for subsequent examinations is of importance, and preliminary experiments were made to determine the most favorable procedure. The collection of sputum was out of the question because bronchial secretions are not raised in the majority of cases. All material was obtained therefore, by swabbing the mucous membrane with sterile cotton swabs placed on iron wire, after the type of the Mathers swab.[19]

All patients were examined clinically by another member of the staff, Dr. W. B. Sharp, who was working at the same time on the epidemiologic and clinical phases of acute upper respiratory infections. I am indebted to Dr. Sharp for all clinical data contained in the present report. Depending on the clinical diagnosis, certain areas of mucous membrane were thoroughly stroked with the swabs.

The first 25 cases included 13 of acute rhinitis, 2 of acute follicular tonsillitis, 5 of acute pharyngitis, and 5 cases which presented involve-

[10] South African Institute for Medical Research (Publications), Dec. 22, 1913.

[11] Jour. Infect. Dis., 1915, 17, p. 514.

[12] Bull. Johns Hopkins Hosp., 1917, 28, p. 306.

[13] Jour. Am. Med. Assn., 1917, 69, p. 2165.

[14] Jour. Lab. & Clin. Med., 1919, 4, p. 484.

[15] Brit. Med. Jour., 1921, p. 259.

[16] Jour. Exper. Med., 1915, 22, p 804.

[17] Ibid., 1919, 29, p. 251.

[18] Proc. Soc. Exp. Biol. and Med., 1916, 14, p. 29; Jour. Immunology, 1917, 2, p. 425.

[19] Jour. Infect. Dis., 1918, 22, p. 523.

ment of the bronchi together with acute inflammation of the upper respiratory tract. In order to obtain data on the most favorable site from which to obtain material, separate swabs were taken from the nose, the nasopharynx and the pharynx. Individual examinations were made for the pneumococcus from each of the swabs so taken, according to the methods outlined later. Briefly, it was found that cultures from the nasopharynx gave the greatest percentage of pneumococci irrespective of diagnosis and indicated that region to be a primary seat of localization for the organism in acute respiratory infections of this class. In cases of rhinitis, throat cultures were found to be of little value, but the nasal cultures on two occasions gave positive results when material was taken well back toward the choanae, while nasopharynx cultures proved negative. In inflammations of the pharynx, larynx and tonsils, nasal cultures proved of no value, indeed cultures from the region of the pharynx were positive for the pneumococcus in only 1 of 6 cases. As a result of these preliminary examinations the following routine procedure was adopted: In cases of rhinitis, the middle fossa and floor of the nostril was swabbed, together with a second swabbing of the nasopharynx. In cases of tonsillitis, pharyngitis, laryngitis and influenza, swabbings were made from the posterior pharynx and from the nasopharynx. Normal persons were swabbed in all three areas, nasopharynx, nostril, and the pharynx. Particular care was taken in all swabbings to prevent salivary contamination. Separate determinations were not made. The two swabs were pooled, and a single determination made from the combined material by injection into mice.

The methods for the demonstration of pneumococcus in the material collected as described offered certain technical difficulties. Early in the studies, the swab was placed in a tube of sterile, warmed Ringer solution, and the mucous secretions brought into suspension by allowing the swab to stand in the warm fluid for about 2 hours with frequent agitation. One c c of the suspension was then injected intraperitoneally into a white mouse. The method first advanced by Blake[20] for the determination of the presence and type of pneumococcus in sputum was then followed, essentially as recommended by him. The results were not satisfactory in that few pneumococci were obtained, and the mortality of the mice was very low. Two swabs were taken from a given area and treated in the same manner as had been the single swab;

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[20] Jour. Exper. Med., 1917, 26, p. 67.

it was hoped thereby to obtain a heavier inoculum. No appreciable improvement could be observed. Finally, the method was modified to include a preliminary enrichment of the material on the swabs, followed by subsequent inoculation of this enriched fluid into mice. This modified method has given excellent results and is essentially as follows:

The two swabs taken from the most promising regions, as determined by clinical examination, the nasopharynx and either the pharynx or nasal cavity, were placed in 5% sheep dextrose blood broth, made according to the method which Avery[21] used in his substitute method for mouse technic in the typing of pneumococci from sputum. Our technic differed only that sheep blood was substituted for rabbit blood. The broth was then incubated for a period of from 8 to 12 hours at 37 C., with agitation of the tube from time to time to insure proper distribution and full benefit from the added blood. This method gives a preliminary enrichment of the pneumococci contained on the original swabs. Stained smears from such broth cultures will ordinarily show a preponderance of pneumococci over the accompanying staphylococci, within the time of incubation used. Following the preliminary enrichment, 1 c c of the broth culture, as free as possible from red blood corpuscles, was injected intraperitoneally into white mice. In cases in which death of the animal did not follow within 24 hours, a peritoneal puncture was made. Smears were made from the fluid withdrawn and, satisfactory growth being evidenced, the animal was killed.

The peritoneal cavity of the mouse was washed according to the method of Blake[20] and the pneumococci typed by agglutination and precipitin tests in the usual manner. Cultures on blood-agar plates were made at necropsy, from peritoneal fluid and from heart blood. The gram-positive, lance-shaped, encapsulated diplococci were later isolated in pure culture, and confirmatory agglutination and bile solubility tests were made with the pure broth culture for final determination of the type of pneumococcus. All aglutination tests were given 2 hours' incubation at 37 C., and a preliminary reading made. They were then placed in the icebox over night and final readings made in the morning. Bile solubility tests, as the final criterion of a pneumococcus, were made by adding one part of ox bile, first filtered and then sterilized by steaming for 3 succeeding days, to 3 parts of a broth culture of the organism. In all instances final diagnosis of organism and type were based on these reactions in pure broth culture.

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[21] Jour. Am. Med. Assn., 1918, 70, p. 17.

The experience of many workers has seemed to indicate that passage of suspected pneumococcus material through a white mouse furnishes probably the most exact technic for its isolation. The animal tissues furnish a favorable environment for the growth of the organism, and in addition the blood stream of the white mouse exercises a more or less specific filtering action on the pneumococcus. Nevertheless, it was felt that careful examination of plate cultures from the swabs might yield even better results. Consequently, in a series of 56 cases, duplicate plate examinations and mouse determinations were carried out. The medium used for the plates was a 5% sheep blood veal infusion agar, reaction PH 7.8.

The plates were inoculated with the swabs and then streaked out in sunburst fashion. After 24 hours' incubation at 37 C., they were examined under the dissecting microscope and 5 green-producing colonies, selected at random from different portions of the plate but showing minute differences in colony structure, were picked to blood agar slants. These were later obtained in pure broth culture and subjected to bile solubility tests. The mouse technic was as previously outlined.

Of the 56 cases subjected to duplicate examinations, 13 proved positive by the mouse method while only 4 gave positive cultures of pneumococci by the plate method. In only one instance was a pneumococcus found by the plate method and not obtained by the mouse technic. The results show that the technic of enrichment and subsequent mouse inoculation is best suited to the isolation of pneumococci present in these conditions. Following these preliminary experiments in the autumn of 1919, the mouse method was employed exclusively in further studies.

THE INCIDENCE OF THE PNEUMOCOCCUS IN NORMAL PERSONS

The incidence of the various types of pneumococci in the pneumonias has been determined for a large number of cases, not only by the original workers, Dochez and Gillespie, but by numerous other investigators previously cited; likewise, data are at hand bearing on the evidence of the organism in normal persons.

Pneumococci are frequently found in saliva. Early studies by Frost, Divine and Reineking[22] demonstrated pneumococci in the saliva of 18 of 50 different normal persons examined, or 36%, although their criteria for determination of the coccus were probably not exact in the light of our present-day knowledge. Study of the sputa from 70 normal persons by Park and Williams[3] demonstrated pneumococci in 51 instances, although the same criticism might apply to their work, in that bile solubility tests were not employed. Stillman,[23] in a comprehensive study conducted some years later, and covering about 297 cases of normal persons, demonstrated the organism in 39% of his cases. The incidence of types was also determined. He found that types 4 and 3 were the most common groups of pneumococcus observed in normal saliva, with atypical type 2 organisms showing a relatively high incidence. The fixed types, types 1 and 2, were found in only a single instance. It would seem that the incidence of the pneumococcus in saliva is relatively high, averaging probably 40%, with certain definite types predominating.

A distinct necessity in the study of an organism concerned in acute respiratory infections is the determination of a mean for that organism in normal persons in sites most subject to acute inflammation. Certain data are available concerning the incidence of the pneumococcus in the nasopharynx and pharynx of such normal persons. Sailer, Hall, Wilson and McCoy[24] studied 700 men in a military command. These men were free from respiratory infection, but had been in more or less contact with prevailing pneumonia. Swabs were taken from the nasopharynx, spread on blood-agar plates, typical colonies picked, and broth cultures subjected to the usual tests of bile solubility and agglutination for type. One hundred and eleven of these cases yielded cultures of the pneumococcus, or 16% of the total. Of the positive findings 5.4% were of type 1, 13.52% were type 2, type 3 constituted 4.5% while 76.58% were found to fall into the type 4 group. A later study of a civilian population by Meyer[25] showed 21 of a series of 100 normal subjects to be carriers of the pneumococcus, or 21%. Of the 21 cultures isolated, none were classified as members of the fixed types 1 and 2. One type 2a strain was identified, while 3 proved to be of type 3. The remaining 17 belonged to the heterologous type 4. Fifty samples of sputum from various persons among a dispensary population were studied by Sydenstricher and Sutton [26] and gave similar results, in that 38% were positive for the pneumococcus, with type 4 predominating.

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[22] Jour. Infect. Dis., 1905, Suppl. 1, p. 298.

[23] Jour. Exper. Med., 1917, 26, p. 513.

[24] Arch. Int. Med., 1919, 24, p. 600.

[25] Jour. Am. Med. Assn., 1920, 75, p. 1268.

A further study of pneumococcus incidence among normal persons by the same methods employed for the study of respiratory infections was felt to be essential, and preliminary to any studies of the nose and throat under pathologic conditions. Briefly, 46 cultures have been made from a group of students in the university who had not at the time been knowingly exposed to colds, or who had themselves suffered from colds within recent date. All were subjected to a careful clinical examination before cultures were taken to rule out possible inflammation of the respiratory mucous membrane. From the cultures derived from 10 of these persons, pneumococci were obtained, 21.7%. The majority of these were type 4, nine of the cultures falling into this group. The other culture was of atypical type 2 variety. Strains representative of the fixed types were not found, nor were strains of type 3 isolated. The swabbed material, even after preliminary enrichment, was in general nonpathogenic, inoculations of 1 c c of the blood broth culture from swabs, producing death of the mice within 24 hours in only 2 instances in the entire series. The incidence of the pneumococcus, then, in the normal respiratory tract was found to be somewhat over 21%, with most of the organisms type 4, and possessing a low grade of virulence.

THE PNEUMOCOCCUS IN COMMON COLDS

The results obtained by a considerable number of investigators previously cited, has led to definite knowledge of the incidence of the different types of pneumococci in pneumonia; likewise, the incidence in normal persons is rather well understood. Few studies, however, have been made on the prevalence of the types of pneumococci in simple acute respiratory conditions. Valentine [27] has probably made the most extensive study of the pneumococcus in common colds. Her investigations were directed toward a determination of the pneumococcus in these simple infections as a possible source of contagion for lobar pneumonia. Cases in her series numbered 65, and pneumococci were recovered from 43 of them. The types were represented by two strains of type 1, two of type 2, four of type 3, while 35 were placed in the heterologous type 4.

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[26] Bull. Johns Hopkins Hosp., 1917, 28, p. 312.

[27] Jour. Exper. Med., 1918, 27, p. 27.

Among the pneumonia cases studied by Clough[12] were included a few cases of acute and chronic bronchitis in which pneumococci were found. Other than these two reports, no information bearing on the frequency of pneumococci in the simpler respiratory conditions could be found in the literature.

In studying the cases of common colds in our series, no attempt was made to select certain types of infection. All cases among a student population were examined as they were reported from time to time. Consequently, they vary considerably in the clinical type of infection. A special effort was made, however, to have cases available early in the onset of the inflammation, and the majority were observed within the first 24 hours of the cold, rarely after a period of more than 48 hours following the onset of symptoms. A total of 77 colds are included in the present series. Briefly, 27 of them showed the pneumococcus when cultivated by the methods outlined. The incidence of the different types of pneumococci is indicated in table 1.

TABLE 1

THE PNEUMOCOCCUS IN COMMON COLDS, TOGETHER WITH THE INCIDENCE OF TYPES OF PNEUMOCOCCI

	Total Cases	Pneumococcus Present	Percentage Showing Pneumococcus	Type 1	Type 2	Type 2a	Type 3	Type 4
Normals	46	10	21.7	0	0	1	0	9
Colds								
Acute rhinitis	47	17	36.2	0	1	2	3	11
Acute pharyngitis	9	1	11.1	0	0	1	0	0
Acute rhinitis and bronchitis	11	5	45.5	1	1	1	0	2
Acute pharyngitis and bronchitis	4	2	50.0	0	0	0	1	1
Tonsillitis	6	2	33.3	0	0	0	0	2
Incidence of pneumococci in all colds	77	27	34.9	1	2	4	4	16
Percentage of incidence of types in positive cases of colds	..	..	....	3.7	7.4	14.8	14.8	59.2

The results presented in table 1 indicate that the pneumococcus is present in a considerably higher percentage of cases of colds than in the series of normal persons examined under the same conditions. No particular variation in the degree of incidence among the various types of inflammation is evidenced, except that in general it may be observed that pneumococci are found more commonly in those cases which show an involvement of the bronchi, together with an inflammation of the nose or pharynx.

By far the most common group of coccus found in normal persons was the pneumococcus 4. This was also the case with pathologic throats, but in these representatives of all of the types were isolated, even the fixed types 1 and 2 being observed.

No attempt was made to determine the exact number of pneumococci in relation to members of the gram-negative, streptococcus and Pfeiffer bacillus groups. Rough plate readings were made, however, and in general, green-producing colonies constituted from one third to three fourths of the total colonies developing on blood-agar plates, inoculated directly with the swabs from the nasopharynx.

A STUDY OF THE PNEUMOCOCCI INVOLVED IN EPIDEMIC SORE THROAT

The cases of acute respiratory infection which have been previously described constitute sporadic cases developing among a typical urban population. In the course of this work, a restricted epidemic of sore throat occurred among the children attending the School of Education of the University of Chicago. The clinical picture of these cases was out of the ordinary. This fact, together with the evident communicability of the infection, attracted attention to the epidemic which apparently was localized in this particular institution. It has been studied intensively by Sharp, Norton and the writer, and a complete report will be given in a later paper. Certain data which are of importance in a general consideration of the relation of the pneumococcus to upper respiratory infections, will be given here briefly.

A series of nine cases was selected from among those first encountered in the epidemic, and examinations were made for a period of approximately three months at weekly or bimonthly intervals. An additional examination was made after the lapse of 4 months, when a recurrence of the pathologic condition developed, following summer vacation.

A type 4 pneumococcus was isolated consistently from all 9 patients throughout the course of the infection and for periods varying from 2 weeks to at least six weeks after all clinical symptoms had disappeared. In several recurrent cases developing after 5 months, in the same institution, pneumococcus 4 was again isolated in most of the cases. Serologic identity of all of these type 4 pneumococci has been proved. This work is described later in the course of this paper.

A number of normal throats, 13 in all, were examined in the course of the study for the presence of pneumococci in order that a control might be obtained on cases of the infection. The results obtained from the examination of 2 such series, selected at random from approximately the same age group and the same school population, showed that the particular organism observed in the pathologic throats was uniformly absent in the normal throats. Pneumococci were demonstrated in several instances, among them four type 4 and two type 2a pneumococci. These type 4 organisms were, however, proved to be serologically distinct from those involved in the epidemic, with a single exception. The latter instance might well be explained on the basis of the individual representing a normal carrier condition.

THE PNEUMOCOCCUS IN INFLUENZA

In the course of our studies on common colds, there occurred in the early months of 1920 a recurrence of the 1918 pandemic of influenza. Work on colds was suspended for the time being, and investigations were confined to a similar study of the incidence of the pneumococcus in influenza. On account of the brief period during which cases were available, only a limited number could be studied. Three separate series were investigated in order that the bacteriology of like conditions in different localities might furnish some basis for comparison and possibly permit a generalization on bacteriologic conditions in this type of infection.

The attention of various investigators had been called to the prevalence of pneumococci in influenza in the epidemic of 1890, and greater or less stress has been laid on its importance in this condition ever since. Even before Pfeiffer[28] called attention to the bacillus which was held for so many years to be the direct etiologic agent in influenza, the pneumococcus had been studied in its relation to the disease. Marmorek[29] was among the first to encounter the pneumococcus in influenza. Weichselbaum,[30] in more searching studies, found the pneumococcus to be among the most frequent invaders. Further evidence concerning the presence of the organism in influenza and its sequelae was furnished by Kirchner,[31] Babes,[32] and Levy.[33] At this time the organism was apparently felt to have no special significance in the direct etiology of the condition. The general inference of all of these workers was essentially that the virus of influenza, whatever it was, merely prepared the way for the entrance of the pneumococcus as a secondary invader.

In the most recent pandemic, that of 1918, a great number of workers found the pneumococcus in cases distributed throughout the country. In certain districts it seemed to be the chief organism involved. Lamb and Brannin[34] found it to be among the more important organisms in influenza at Camp Cody. The extended study by Hirsch and McKinney[35] at Camp Grant indicated the pneumococcus to be the chief organism involved in cases occurring at that post during the height of the epidemic. Later studies[36] on postepidemic cases, however, demonstrated a high incidence of hemolytic streptococcus infections, less frequently pneumococcus. In general, one may say that all workers recognized the pneumococcus as constituting one of the three or four more important groups of bacteria concerned in the infection. In some localities, it was the dominant species.

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[28] Deutsch. med. Wchnschr., 1892, 18, p. 28.

[29] Wien. klin. Wchnschr., 1890, 3, p. 143.

[30] Ibid., p. 104.

[31] Ztschr. f. Hyg. u. Infektionskr. 1890, 9, p. 528.

[32] Centralbl. f. Bakteriol., 1890, 7, p. 233.

[33] Berl. klin. Wchnschr., 1890, 27, p. 143.

The group of cases included in the present report is derived from three different sources. A number of cases developed among the same general student population at the University of Chicago from which we had been drawing our material for the study of common colds. A group of cases occurring at the Great Lakes Naval Training Station constituted our second series, while the third series was obtained from soldiers stationed at Camp Grant, Rockford, Ill. The results of the examinations from these three series of influenza cases are contained in table 2.

TABLE 2

THE PNEUMOCOCCUS IN INFLUENZA

	Total Cases	Pneumococcus Present	Percentage Showing Pneumococcus	Type 1	Type 2	Type 2a	Type 3	Type 4
Great Lakes	17	6	36	1	3	1	1	0
Camp Grant	12	4	33	0	0	0	0	4
University of Chicago	8	4	50	0	0	0	1	3
Incidence of pneumococci in all cases	37	14	38	1	3	1	2	7
Percentage of incidence of type pneumococcus in positive cases	..	..	..	7	21	7	14	50

Although the total number of cases is too small to warrant definite conclusions, the results indicate in a degree that the presence of the fixed types is considerably more common in influenzal conditions than in common colds. It even approaches somewhat the type incidence usually encountered in lobar pneumonias. Pneumococci were not present in influenza cases much more commonly than in common colds. Data on cases of cold showed an incidence of 34%, in influenza, 38%. The organism was present about twice as frequently in influenza as it was in the series of normal persons studied.

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[34] Jour. Am. Med. Assn., 1919, 72, p. 1056.

[35] Jour. Infect. Dis., 1919, 24, p. 594.

[36] Ibid., 1919, 25, p. 393.

AN ATTEMPT TO DETERMINE THE SPECIFIC RELATIONSHIP OF THE PNEUMOCOCCUS TO COMMON COLDS

Experimental data have been presented which furnish evidence of the presence of the pneumococcus in common colds and influenza, and furthermore indicate that in normal persons these organisms can be found in about 21% or more of cases. It seemed desirable to obtain information bearing on certain fundamental questions. Is the particular pneumococcus which is found in such an acute respiratory infection merely present, more or less accidentally, as a normal inhabitant of the tract at the time of the developing infection? If so, does it evidence any activity, any symbiotic relationship to the infecting bacterium or virus during the course of the infection? If not, does it gain entrance into the inflamed area coincidently with developing symptoms, previous to that time, or somewhat later in the course of the infection? Does it disappear soon after the subsidence of clinical symptoms, or may it persist for appreciable lengths of time, constituting a carrier condition, permanent or temporary? With these questions in mind, a group of 10 normal persons was selected, and each one was subjected to daily routine cultures over a period of about two and one-half months. Each case was watched closely for the onset of any symptoms which would indicate an oncoming cold. Detailed daily studies of each culture were not made after the initial culture, except when colds developed. But from time to time, at intervals of perhaps two weeks, such examinations were made in order to maintain a general idea of the constitution of the flora. The plates were critically examined each day, however, and a percentage estimate made of the different types of colonies which developed.

During the course of these experiments, 5 of the 10 subjects in the series developed one or more colds, the other five remaining normal throughout the period of observation. Among the persons who maintained a normal condition of the upper respiratory tract, different conditions were observed as regards the pneumococcus.

Subject A-4 gave cultures of the pneumococcus of the type 4 variety on the initial examination, and this organism persisted in subsequent cultures over a period of 2 months, green producing cocci being the predominating organisms in the flora continuously. It then disappeared and further cultures proved negative.

Early plate readings of A-5 showed the absence of green producing cocci in the flora. Fifteen days after the first examination, green colonies became dominant on the plates. Cultural tests showed that they included pneumococcus 4. They continued in the throat until 2 months after the beginning of the study of the case, when B. mucosus capsulatus became dominant, and indeed crowded out the green-producing colonies. Cultures taken after this time yielded no pneumococci.

The group of green-producing cocci was the predominating type of organism in the cultures from A-7 throughout the course of the study. Pneumococcus 4 was identified.

Subject A-8 was characterized by the presence, largely, of only 2 of the general groups of respiratory micro-organisms during the period of examination, namely, green-producing cocci and organisms of the Micrococcus catarrhalis group. No pneumococci were isolated at any time.

The flora of A-10 was found to be subject to considerable variation. Early in the course of the experiments, the Mirococcus catarrhalis group predominated, with the greens numerically next in order. Two months after the first examination, the greens increased markedly in numbers and pneumococci belonging to type 4 were isolated. This condition was only transitory, however, for soon the Pfeiffer bacillus dominated all plates with the pneumococcus no longer capable of being demonstrated in culture.

It would seem, then, that the flora of the normal person, at least during the winter months, is subject to distinct variations in constitution from time to time. One type of organism may dominate in a given respiratory tract for varying lengths of time, to be eventually supplanted by another. In 4 of the 5 cases studied, the pneumococcus was found at one time or another. It persisted in a given throat for as long as 2 months or more, and constituted a distinct carrier condition. Again, it was present in demonstrable numbers for a few days only, with subsequent replacement by other species of bacteria. In these 5 cases the pneumococcus came and went, or persisted indefinitely, without the development of clinical symptoms.

Somewhat more uniform conditions are evidenced among the 5 patients who developed colds in the course of the experiments. Green producing cocci were present in the upper respiratory tract of A-1 from the time of the original culturing, and extending over two months time. Pneumococci were, however, not present, the green-producing cocci being Streptococcus viridans. The average incidence varied from 20 to 50% per cent of the total flora, as evidenced by plate cultures. Occasionally green colonies dominated the plates to the practical exclusion of all other forms. Two weeks after initiating cultures, an acute pharyngitis developed. Pneumococci were not demonstrated in the course of the cold. About 2 months after the original culturing, a second acute pharyngitis was manifest. The first day on which symptoms were present no pneumococci were present in cultures, and the percentage of greens had not noticeably increased. The second day's culturing gave the same bacterial picture. On the third day, however, pneumococcus 4 was isolated. It was absent in cultures taken one week later, although slight symptoms of the cold persisted.

Two colds developed in the course of the study of A-2. Symptoms of a beginning rhinitis were present on the second day after study of the case had been initiated. Pneumococci could not be isolated throughout the course of the cold, which lasted 8 days. Three weeks later a second rhinitis developed, and this time a pneumococcus 4 was obtained from cultures taken on the first day that symptoms of the inflammation were present. The organism persisted in cultures taken during the course of the cold but disappeared with the subsidence of the infection.

A-3 likewise developed an actue rhinitis the second day after the beginning of the investigation. Eight complete examinations were made during the course of the infection, but the pneumococus could not be demonstrated in culture. Six weeks after the first infection, a second rhinitis was observed. A culture was not obtained until the second day after the beginning of the cold, but at that time the pneumococcus 4 was found in large numbers. During the four days on which symptoms were manifest, the organism was demonstrated each day, and it continued in cultures for 10 days thereafter. Following that time it remained negative during the 3 successive observations.

Green-producing cocci were uniformly in the minority in cultures taken from A-6, oftentimes being absent. The gram-negative cocci and staphylococci were the predominating organisms in the flora. Three weeks after the first culture, an acute rhinitis was diagnosed. The Pfeiffer bacillus seemed to be the organism chiefly involved. Pneumococci were not isolated from any of the cultures taken during the study of this case.

The fifth subject who developed a cold while under observation was A-9. Green-producing cocci were consistently the predominating type in cultures, usually constituting about 90% of the colonies developing on blood-agar plates, but no pneumococci could be determined. Three weeks after the initiation of the study, a slight rhinitis followed. A type 4 pneumococcus was cultivated on the first day that symptoms appeared, but it disappeared from cultures soon, and subsequent cultures were negative for the organism.

Analysis of the last 5 cases brings out certain facts. Certainly the pneumococcus was not involved in the etiology of all of the colds developing in the series. The first colds of subjects A-2 and A-3 could not be connected in any way with an etiology involving that organism; nor could the cold which was observed in A-6. The second colds occurring in both A-2 and A-3, as well as the rhinitis which was observed in A-9, may have been of pneumococcal origin. In these 3 cases of rhinitis, the pneumococcus was present in cultures coincidently with the onset of symptoms. As regards the second cold of A-1, the question is problematical, but most likely the pneumococcus isolated in that instance can best be interpreted as a secondary invader. One cannot, however, definitely ascribe a pneumococcal origin to even these 3 cases, for there is no direct knowledge of the period of incubation of such infections. The presence of the pneumococcus at the time of infection may have meant merely that under the stimulus of the exciting agent of the cold, pneumococci normally in the throat, although present in such small numbers that they could not be demonstrated, rapidly began to multiply, and possibly acquired as well a distinct pathogenicity. Thus one cannot determine whether the presence of the organism indicates direct etiology or symbiotic relationship to the infection.

From the study of this series of cases, then, one is led to conclude that intermittently normal persons may develop either a temporary or even chronic carrier condition for Fränkel's pneumococcus, without the organism causing any symptoms of pharyngeal or nasal inflammation A certain percentage of colds may be due to the invasion of the respiratory tract by the pneumococcus since, in the cases cited, pneumococci have been demonstrated not to be present in the normal condition of the nose and throat. Furthermore, evidence of a beginning inflammation was present coincidently with their determination in culture. In other circumstances it appears that the organism invades the inflamed area secondarily to some other organism which has primarily incited the infection.

THE EXTENT OF THE CARRIER CONDITION FOR THE PNEUMOCOCCUS

During the course of the study of the "A" series of cases previously described, it was observed that a given pneumococcus was carried in the throats of persons a relatively short time following convalescence from these simple types of respiratory involvement, acute rhinitis and pharyngitis. Ten days was the longest time observed in the cases studied. These few cases would indicate that there is little danger of spread of contagion from the convalescent.

In the cases of epidemic tonsillitis and pharyngitis described previously, the School of Education Series, the convalescents maintained the carrier condition for a much longer time. The majority of the 9 patients in this series revealed the pneumococcus in examinations following the infection for at least 6 weeks, most of them 2 months or longer, while in 3 patients it persisted for at least 7 months. It must be remembered, however, that this was an unusual type of respiratory involvement and, moreover, the particular pneumococcus 4 was distinct from any other subgroup of pneumococcus 4 isolated in the course of our studies on colds.

Attention was directed to the possibility of a certain percentage of normal persons constituting a population of permanent pneumococcus carriers. A series of normal persons was studied in order to ascertain whether the carrier state as observed in normal persons was transitory in type or was as a rule long continued. Six subjects were examined during the spring months, April and May, while a second group of 5 were studied intensively during the early winter months, Nov., Dec., and Jan. Four cases of the Spring series, when examined at weekly intervals, did not at any time give evidence of pneumococci of any type. Two cases did present pneumococci at some time during the experiments. One subject, C623, was positive at the first examination, and continued to give cultures of type 4 pneumococcus for three weeks, after which the cultures were negative. The second subject, C492, proved negative for pneumococcus at the first examination but one week later cultures were positive. Cultures were still positive about 7 weeks later when conditions prevented further study.

Of the series of 5 normal cases studied during the early winter months, 4 at some time or other picked up the organism, although all were initially negative. A temporary carrier condition developed, respectively, for periods of 2 months, 2 months, 1 week, and 3 weeks, in the 4 cases.

The limited number of cases studied forbids definite conclusions. Indications are that protracted carrier condition of the pneumococcus is rare but that temporary carriers develop with considerable frequency, probably more commonly in winter months than during the spring and summer. Based on the cases studied, the average time of the carrier state is about one month.

SEROLOGIC STUDY OF TYPE 4 CULTURES TAKEN FROM PERSONS WITH COLDS, FROM NORMAL PERSONS AND FROM PERSONS WITH INFLUENZA

Pneumococcus 4 has been by far the most common pneumococcus observed in our study of acute respiratory infections. Previous studies cited have shown a decided variation in the relation of any one strain of the type 4 pneumococcus to another, and indeed the group is recognized as a collection of heterologous strains having little serologic relationship. So common, however, was its occurrence in our cases of various clinical type, that if any particular organism, for example the pneumococcus, was to be given any weight in a determination of a common etiology, some specific relationship necessarily had to be demonstrated between these various strains. In other words, was a single variety of pneumococcus 4 involved, or did the various strains differ in biologic properties?

Fifteen strains were selected from type 4 pneumococci isolated from various types of acute respiratory involvement and from normal persons. These 15 cultures, representing type 4 pneumococci present in normal persons, in cases of influenza, and in various types of common colds, have been studied intensively.

Monovalent rabbit serums were prepared for these 15 strains by injecting the animals with cultures of pneumococci grown on blood-agar slants and washed off in salt solution. Killed cultures were used in the early injections and were given intravenously for 3 successive days, followed by a like period of rest. Later live cultures were employed. As a general rule, about 20 inoculations were required to obtain a relatively high agglutination titer for the coccus. All serums so prepared, agglutinated the homologous strain in a dilution of at least 1:600, some as high as 1:1,600. After a sufficiently high titer had been obtained, the rabbits were bled to death, and the serum preserved in frozen ampoules. Serum so preserved will not show a decided drop in agglutinating power for some time. One serum, stored for 9 months, had lost only 30% of its agglutinating value.

All 15 strains were tested by agglutination with each of the immune serums so prepared. The agglutinating titer for the homologous strain, as well as cross agglutination with other strains, was determined for each serum. The tests were made by adding 1 c c of a young broth culture of pneumococci to an equal volume of diluted serum. Control tests included monovalent horse serums for types 1, 2 and 3, in dilutions of 1:40, 1:40 and 1:20, respectively, a normal rabbit serum control, in a final dilution of 1:25, and a saline control. The tests were incubated at 37 C. for 2 hours, preliminary readings made, and the tubes placed in the icebox over night. Final results were recorded from readings made the following morning.

TABLE 3

CROSS AGGLUTINATION OF TYPE 4 PNEUMOCOCCI *

Culture	Source	Monovalent Rabbit Serums														
		C623-4	C492-7	E-24	E-27	G4	G6	C627	C628	C230	C201	C163	C504	C548	C235	C114
C623-4	Normal......	800	—	—	—	—	—	—	—	—	—	—	50	—	—	—
C492-7	Normal......	—	1200	—	—	—	—	—	—	—	—	—	—	—	—	—
E-24	Normal......	—	—	800	—	—	—	—	—	—	—	—	—	—	—	—
E-27	Normal......	—	—	—	800	—	—	—	—	—	—	—	—	—	—	—
G-4	Influenza....	—	—	—	—	1000	200	—	—	—	400	—	—	—	—	—
G-6	Influenza....	—	—	—	—	300	1200	—	—	—	50	—	—	—	—	—
C 627	Influenza....	—	—	—	—	—	—	1600	—	—	—	—	—	—	—	—
C 628	Influenza....	—	—	—	—	—	—	—	600	—	—	—	—	—	—	—
C 230	Acute rhinitis.........	—	—	—	—	—	—	—	—	1000	—	—	—	200	—	—
C 201	Acute rhinitis.........	25	25	—	—	400	200	—	—	—	800	—	25	100	—	25
C 163	Acute rhinitis and bronchitis..	—	—	—	—	—	—	—	—	—	—	1000	—	—	400	—
C 504	Acute rhinitis.........	100	—	—	—	—	—	—	—	—	—	—	800	—	—	—
C 548	Acute rhinitis.........	—	—	—	—	—	—	—	—	300	—	—	—	600	—	—
C 235	Tonsillitis...	25	—	—	—	—	—	—	—	—	—	200	—	25	800	—
C 114	Acute rhinitis.........	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1200

* Figures represent highest agglutinating titer; — = absence of agglutination.

Control tests were all negative with the exception that strain C201 was agglutinated by type 1, 2 and 3 monovalent horse serums. The normal rabbit serum and saline controls for this strain were negative.

The cross agglutination experiments indicate common properties peculiar to certain of the organisms studied. Final group classification and identity of strains was proved by the use of the agglutinin absorption technic. Those serums which showed agglutination with strains other than the specific organism used in its preparation, were absorbed by the cross agglutinating organism, and the absorbed serum then tested by agglutination for the persistence of agglutinins for the homologous pneumococcus.

The technic of agglutinin absorption was as follows, essentially that used by Avery [16] in his study of atypical type 2 strains. The washed bacterial residue from 150 c c of an 18-24 hour old broth culture was added to the undiluted serum. Before adding the organisms, they were killed by heating to 55 C. for one-half hour. The mixtures were incubated at 37 C. for 2 hours with frequent agitation, and then were placed in the icebox over night. The serum was then freed of bacteria by centrifugation, and the supernatant fluid pipetted off. This absorbed serum was used for agglutination tests with the homologous organism for the presence or absence of agglutinins. The technic was controlled by the absorption of the serum by the homologous organism as well, with agglutination tests following, in order to assure that the amount of bacterial residue used was sufficient to remove all agglutinins.

By these methods it was determined that certain of these type 4 strains fell into restricted groups. Strains G4 and G6 from the Camp Grant epidemic of influenza and strain C201 from a case of rhinitis in the Chicago series proved to be allied. Contact between the three patients was unlikely with the exception of the 2 patients with influenza. Likewise, strains C163 and C235, isolated respectfully from cases of acute rhinitis and bronchitis, and from acute tonsillitis, were found to constitute a second small group. Strains C230 and C548 also possessed like serologic properties. No relationship could be established between C504, a rhinitis strain and C623-4, a normal strain, although cross agglutination had occurred. Agglutination had been due apparently to minor agglutinins. Strains C492-7, C623-4, E24, E27, C627, C628, C504 and C114, all differed in biologic properties.

Immunologic experiments on the predominating type of pneumococcus isolated in the course of this study show that there is little relationship between such strains encountered in various acute respiratory conditions. Of the 15 studied, 8 were entirely distinct one from the other. Grouping could be effected in 3 instances, one group including 3 of the strains studied, the others 2 each. It seems certain that there is little relationship between the type 4 pneumococci encountered in the acute infections of the upper respiratory tract. In the light of studies made on type 4 pneumococci occurring in lobar pneumonia, this was logically to be expected.

Distinctly different results have been obtained in a study of the group 4 strains obtained from those cases of epidemic tonsillitis and pharyngitis previously described, which occurred in the School of Education at the University. Common agglutinating properties were found to exist between all strains isolated from the original 9 cases studied, as well as from 2 others observed later. A monovalent rabbit serum prepared from strain E4-6 agglutinated all of the strains mentioned in the foregoing. Cross agglutination was not obtained with type 4 strains from other respiratory infections or from normal sources. Control tests with the fixed types were likewise negative. Serologic identity of all these strains was thus established.

In general, then, one may conclude that the pneumococci which are encountered in various types of respiratory involvement are unrelated. There is no common strain which is involved in the etiology of these infections, and no specific etiology may be claimed for the pneumococcus. In isolated instances, however, such as the epidemic at the School of Education, a common strain of pneumococcus may be involved in a given group of cases.

THE COMPARATIVE VIRULENCE OF PNEUMOCOCCI ISOLATED FROM NORMAL THROATS AND FROM THROATS AFFECTED BY ACUTE RESPIRATORY CONDITIONS

The observation was made during the study of material from various sources by the mouse method that a difference in degree of pathogenicity for these animals was apparent. Cultures from normal throats which were later proved to contain pneumococci had little effect and indeed rarely produced death of the animal within 2 or 3 days. Cultures from patients with cold differed. A few would cause death of the mice in 24 hours or thereabouts, but most of them had a decidedly lesser effect. During the study of influenza cases it was apparent that the organisms involved were much more virulent for mice.

Of course the original injections given the animals contained a variety of organisms besides the pneumococcus, and the variation in lethal effect therefore could not definitely ascribed to a difference of virulence among the pneumococci themselves. For this reason a comparative study of pure strains of pneumococci from various sources has been made. It is well known that the virulence of the pneumococcus varies greatly according to the length of time it has been carried in artificial culture. It gradually decreases in virulence. Likewise its virulence for a given species can be enhanced by frequent passage through that animal. In order that results might be directly comparable, all of the tests for virulence have been made by using blood-agar cultures having the same history. These pneumococci, after removal from the throat, had undergone one mouse passage, had been cultivated on blood-agar plates and then picked to blood-agar slants. They were, then, in the second generation on artifical medium after a single mouse passage. By this method, conditions were exactly comparable and, furthermore, tests for virulence were made within the shortest possible time following removal of the organism from the throat.

In obtaining cultures for inoculation, care was taken to seed as nearly as possible the same extent of blood-agar medium. Growths were washed off in 5 c c of warm sterile broth, and appropriate dilutions made in broth so that the final inoculum was contained in 0.5 c c volume. Mice were inoculated at once intraperitoneally. The results obtained with cultures from normal persons, from patients with colds and from patients with influenza are given in table 4.

TABLE 4

COMPARATIVE VIRULENCE FOR MICE OF PNEUMOCOCCI ISOLATED FROM VARIOUS SOURCES *

Culture	Source	Type of Pneumococcus	Amount of 24-Hour Blood-Agar Slant			
			0.01	0.001	0.0001	0.00001
C623-4	Normal	IV	S	S	—	—
C492-7	Normal	IV	S	S	—	—
E 22	Normal	IV	S	S	—	—
E 28	Normal	IV	S	S	—	—
G 4	Influenza	IV	D14	D15	D60	S
G 6	Influenza	IV	D14	D48	S	S
C 504	Acute rhinitis	IV	D14	D48	S	S
C 548	Acute rhinitis	IV	S	S	S	S
GL 10	Influenza	II	D14	D13	D14	D60
GL 12	Influenza	II	D12	D14	D14	D22
C 230	Acute rhinitis	IV	D48	S	S	S
C 201	Acute rhinitis	IV	D30	S	S	S
C 163	Acute rhinitis and bronchitis	IV	D12	D36	S	S

* S = survived 72 hours; — = not tested; figures represent number of hours before death.

Pneumococci from normal throats uniformly failed to cause death of the mice within the period of observation, even with the largest doses used. Cultures derived from patients with influenza were considerably more virulent than those from normal persons, even in comparison with the same group of organism, type 4. Likewise cultures from persons with colds possessed a higher degree of virulence than type 4 cultures from normal throats.

DISCUSSION

Pneumococci are observed in various simple inflammations of the upper respiratory mucous membrane, grouped together under the general term of "common colds," somewhat more frequently than in throats which do not show lesions, although the increased percentage incidence to the particular region affected, namely rhinitis, pharyngitis, tonsillitis to the particular region affected, namely rhinitis, phayngitis, tonsillitis or combinations of these conditions with bronchial involvement, do not show any appreciable degree of difference in the frequency with which pneumococci are encountered. If any conclusions may be drawn from the limited number of cases studied, it would appear that the organism is somewhat more common in infections which include involvement of the bronchi.

In patients with influenza, pneumococci are frequently encountered, but again in numbers not much greater than in normal persons, and slightly increased over the incidence in common colds. The frequent occurrence of fixed types is chiefly of interest in comparison with the types of pneumococci found in common colds and in normal persons.

While the patient with the average common cold or influenza will only show the presence of the pneumococcus in somewhat greater frequency than the ratio of 1 : 3, nevertheless outbreaks of respiratory infection may occur in which this particular coccus is involved in practically all cases. Such an instance was demonstrated in our School of Education series.

By observing the bacterial changes evidenced in oncoming colds, it was found that in certain instances pneumococci appear in the throat practically at the same time that developing symptoms are observed. Since there is no exact knowledge of the period of incubation in common colds, one can merely conjecture as to the significance of the pneumococci present. If common colds present the relatively short incubation period which we know is characteristic of influenza, then it would seem that in some cases this organism may be the direct causative factor. In other instances, the presence of the pneumococcus in the inflamed area was demonstrated relatively late in the course of the infection. It would seem to be present in such cases as a secondary invader.

Serologic studies of pneumococci, involving type determinations of the organisms from pathologic throats and a more careful study of the predominating group, type 4, give evidence that no one variety of pneumococcus is concerned in those cases in which the organism is present in one capacity or another.

Interesting information is furnished by the study of the relative virulence of pneumococci from various respiratory infections and from normal sources in respect to their relationship to disease. Our early individual case studies and the results obtained in our "A" series in which developing colds were observed both pointed to the conclusion that the pneumococcus certainly could not be involved in the etiology of all colds. The serologic study of various strains obtained from those cases in which pneumococci were found led to the definite conclusion that no common etiology can be proved, for the strains vary decidedly in biologic properties. What, then, is the province of the pneumococcus in these infections, or has it really no significance? Some light is cast on the problem by the virulence studies. Pneumococci from cold sources are surely more virulent for mice than are like cultures derived from normal persons. In other epidemics, such as influenza, it shows a still more heightened virulence.

Granting the fact that the pneumococcus may only play a primary etiologic rôle in a small percentage of cases, as indicated by the studies of our "A" series, still it would seem that the pneumococcus may rather commonly be a secondary invader; or, if present normally in the throat in numbers too small for detection, may increase rapidly in numbers, and under the stimulus of the conditions generated by the inflammation, or a symbiosis with the infecting virus, acquire an increased virulence. It seems probable that in a considerable percentage of upper respiratory infections the pneumococcus is in reality pathogenic, and exercises a real influence in the course of the infection.

CONCLUSIONS

The average incidence of the pneumococcus in normal throats, in the present series of cases is about 21%. Cases of common colds showed pneumococci more commonly, 35%, and the same was true of influenza, 38%.

Type incidence of pneumococci in normal persons and in persons with colds was characterized by the infrequent occurrence of the fixed types of pneumococci. Fixed types are somewhat more frequent in influenza than in other acute infections of the upper respiratory tract.

No serologic relationship could in general be demonstrated between the pneumococci found in these infections. Types other than 4 were observed. Type 4 strains in this series show a division into 8 different strains and 3 small groups. No common strain of pneumococcus was present in acute respiratory infections.

A particular group of cases occurring in a localized epidemic showed a uniform occurrence of the pneumococcus in practically all of the cases studied, a type 4 pneumococcus. The strains were proved to be serologically identical. It seems certain, then, that although the general statement can be made that pneumococci are not found in the majority of colds, and that when they do occur they are rarely related to each other, nevertheless instances occur in which a single type of pneumococcus is involved in all cases of a given group.

Comparative virulence tests showed that the pneumococci from colds and from influenza were more pathogenic than the strains from normal throats.